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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,387	02/01/2002	David Robert Greaves	1430-276	8909

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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/060,387	GREAVES, DAVID ROBERT	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 23-35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 23-35 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 01 February 2002 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/171,802 .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 0202 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's preliminary amendment filed on 2/1/02 has been entered.

Applicant's preliminary amendment filed on 5/14/03 has been entered. Claims 1-22 have been cancelled. New claims 23-25 have been added. Claims 23-25 are pending and are under current consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/171,802, filed on 10/26/98.

Claim Objections

Claim 29 is objected to because of the following informalities: it appears that the term "an" in line 1 should be the term "a". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 31 and 35 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 31 is directed to precursors of macrophages, monocytes, and dendritic cells. Precursor cells are interpreted to read on progenitor cells, the scope of which can

be interpreted to encompass a human embryo. A human embryo is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial for claim 31. See 1077 O.G. 24, April 21, 1987.

Claim 35 is directed to transformed mammalian stem cells and progenitor cells, the scope of which with regard to the progenitor cells can be interpreted to encompass a human embryo. A human embryo is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial for claim 35. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a polynucleotide fragment having at least 90% identity to the polynucleotide of SEQ ID NO: 2, an expression cassette comprising the same sequence, an expression vector comprising the same expression vector, a host cell comprising the same vector, and a process for producing a polypeptide comprising culturing the same host cell.

The nucleotide sequences that have at least 90% identity to the nucleotide sequence set forth in SEQ ID NO: 2, encompassed within the genus of nucleotide molecules of SEQ ID NO: 2 have not been disclosed. Based upon the prior art there is expected to be variation among the species of DNA molecules within the genus of nucleotide molecules of SEQ ID NO: 2 because the sequence of DNA molecules set forth in SEQ ID NO: 2 would be expected to vary among individuals. The specification discloses isolation of a nucleotide sequence (SEQ ID NO: 2) from a human CD68 gene that functions as a transcriptional regulatory sequence and does not disclose other mammalian DNA molecules or other human DNA molecules or other DNA molecules from other cell types encompassed within the genus of nucleotide molecules of SEQ ID NO: 2. There is no evidence on the record of a relationship between the structure of any nucleotide molecule that is at least 90% identical to the nucleotide sequence set forth in SEQ ID NO: 2 and the nucleotide sequence set forth in SEQ ID NO: 2 that would provide any reliable information about the structure of other DNA molecules within the genus. There is no evidence on the record that the nucleotide sequence set forth in SEQ ID NO: 2 had a known structural relationship to any other DNA molecules; the specification discloses only a single human DNA as set forth in SEQ ID NO: 2; the art indicated that there is sequence variation between DNA sequences of CD68 genes. There is no evidence of record that would indicate that any of the claimed variants of SEQ ID NO: 2 even have the function of a transcriptional regulatory sequence. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of

the genus, because a human nucleotide sequence as set forth in SEQ ID NO: 2 is not representative of the claimed genus. Consequently, since Applicant was in possession of only the nucleotide sequence set forth in SEQ ID NO: 2 and since the art recognized variation among the species of the genus of CD68 genes, the nucleotide sequence set forth in SEQ ID NO: 2 was not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of nucleotide molecules of SEQ ID NO: 2 as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claims 29-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a vector comprising a transcriptional regulatory sequence, a heterologous gene and a locus control region, wherein the locus control region (LCR) is located within a region extending from 2940 bp upstream to 335 bp downstream of the CD68 gene, in particular the LCR is located within a 3KB BstXI-BstXI locus immediately upstream of the CD68 gene. The claims are further directed to a mammalian host cell transformed with the same vector and a method of producing a

polypeptide comprising culturing the same host cell and a method of modifying mammalian stem cells and progenitor cells comprising transfecting cells with the same vector.

The nucleotide sequences that encode all CD68 genes encompassed within the genus of CD68 nucleic acid molecules have not been disclosed. Based upon the prior art there is expected to be variation among the species of DNA molecules, which encode CD68, because the sequence of DNA molecules would be expected to vary among individuals. The specification discloses isolation of a nucleotide sequence (SEQ ID NO: 3) that encodes a human CD68 and does not disclose other mammalian CD68 DNA molecules or human CD68 DNA molecules or other CD68 DNA molecules from other cell types. There is no evidence on the record of a relationship between the structure of any CD68 DNA molecule and the human CD68 DNA molecule described in the instant specification that would provide any reliable information about the structure of other CD68 DNA molecules within the genus. There is no evidence on the record that the asserted human CD68 DNA molecule described in the instant specification had a known structural relationship to any other CD68 DNA sequences; the specification discloses only a single human CD68 DNA molecule obtained; the art indicated that there is variation between CD68 DNA sequences. There is no evidence of record that would indicate that any of the claimed variants of the human CD68 DNA molecule embraced by the claims even have the biological activity of the described CD68 molecule. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes

possessed by member of the genus, because a human CD68 DNA sequence is not representative of the claimed genus. Consequently, since Applicant was in possession of only the human CD68 DNA molecule and since the art recognized variation among the species of the genus of CD68 DNA molecules, the human CD68 DNA molecule was not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of CD68 DNA molecules as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Upon further consideration of Applicant's explanation, received in the preliminary amendment of 2/1/02, regarding the differences between the old SEQ ID NO: 2 and the newly disclosed SEQ ID NO: 2 (received on 11/1/01 it has been determined that there is not adequate support in the instant specification for the changes made to SEQ ID NO: 2 as set forth in the sequence listing of 11/1/01. See the new matter rejection below.

New Matter

Claims 23-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states

that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The claims are directed to a polynucleotide fragment having at least 90% identity to the polynucleotide of SEQ ID NO: 2, an expression cassette comprising the same sequence, an expression vector comprising the same expression vector, a host cell comprising the same vector, and a process for producing a polypeptide comprising culturing the same host cell. The claims are also further directed to a polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO: 2.

In the preliminary amendment filed on 2/1/02, Applicants requested entry and examination of a revised sequence as set forth in SEQ ID NO: 2, submitted in parent application 09/171,802 on 11/1/01, that does not contain a five nucleotide fragment that is present in original SEQ ID NO: 2. See pages 5-7 of the amendment received on 2/1/02.

However, the specification provides no implicit or explicit support for revised SEQ ID NO: 2. In particular, the specification has not provided support for deleting the five nucleotide fragment to create revised SEQ ID NO: 2. The specification has only provided support for SEQ ID NO: 2 as originally filed. Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), MPEP 714.02, 3rd paragraph, last sentence and also MPEP 2163.07, last sentence.

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement.

In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure* [or point to case law supporting incorporation of such a limitation as in the instant case]".

Claims 23 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 2, does not reasonably provide enablement for other sequences within the genus of SEQ ID NO: 2 molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a polynucleotide fragment having at least 90% identity to the polynucleotide of SEQ ID NO: 2, an expression cassette comprising the same

sequence, an expression vector comprising the same expression vector, a host cell comprising the same vector, and a process for producing a polypeptide comprising culturing the same host cell.

The specification has taught the nucleotide sequence set forth in SEQ ID NO: 2.

The specification has not taught any nucleotide sequences having at least 90% identity to SEQ ID NO: 2 (termed variants hereafter) that function as a transcriptional regulatory sequence. The skilled artisan would not be able to predict the structure of a variant that is biologically active because the specification has not provided any information as to the structural elements required for a variant to be biologically active. The specification does not provide any information on what nucleotides are necessary and sufficient for biological activity. The specification also provides no teachings on what nucleotide sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a variant nucleotide sequence that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity of the sequence. Since there are no examples of a variant known to have structural homology with SEQ ID NO: 2, it is not possible to even guess at the nucleotides which are critical to its structure or function based on sequence conservation. Furthermore, it is known in the art that nucleotide substitutions can adversely affect biological activity if nucleotides that are critical for such functions are substituted. Even a single base substitution can affect the ability of a nucleotide sequence to function as a transcriptional control element. Huang et al (PNAS, 1998, 95: 14669-14674) support this observation. Huang et al report that a single base

mutation in an enhancer element repressed transcription of the human ζ-globin gene in a transgenic mouse study. See abstract and pages 14669, and 14672. Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives to obtain biologically active variant transcriptional regulatory sequence with a nucleotide sequence differing from SEQ ID NO: 2 since the nucleotide sequence of such variants could not be predicted. Removal of the 90% identity language may be sufficient to overcome this rejection.

It would have required undue experimentation to predict the structures of variants to the claimed sequences that would be biologically active in the absence of a functional assay, without a reasonable expectation of success.

Claims 31-32 and 34-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mammalian host cells transformed *in vitro* with a vector of the claimed invention and a method of modifying mammalian stem cells and progenitor cells *in vitro*, does not reasonably provide enablement for all mammalian host cells transformed *in vivo* with a vector of the claimed invention and methods of modifying mammalian stem cells and progenitor cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to transformed mammalian host cells, wherein the host cell can be a macrophage, monocyte, dendritic cell, stem cell or progenitor cell. The

claims are further directed to a method of modifying mammalian stem cells and progenitor cells.

The specification has taught transformation of mammalian cells in vitro with a vector comprising a locus control region located within a region extending from 2940 bp upstream to 335 bp downstream of the CD68 gene. See the specification at pages 21-28. The specification has contemplated that such a vector could be used to transform somatic cells *in vivo* or *ex vivo* for therapeutic purposes. See pages 28-35. The specification however has not provided specific guidance or working examples that exemplifies or otherwise correlates *in vivo* or *ex vivo* transformation of mammalian cells with therapy of any disease. The teachings, guidance and working examples provided by the instant specification do not enable the skilled artisan to express any heterologous gene under the control of the locus control region of the claimed invention in a host cell *in vivo*. Furthermore, it is unclear what other purpose creating such a host cell *in vivo* would serve other than to provide therapeutic benefit. As such it would have required undue experimentation to make and use the invention as claimed in light of the teachings of the specification.

The claims are directed to mammalian host cells transformed with a vector of the claimed invention and a method of modifying a mammalian stem cell or progenitor cell comprising transfecting the cells with a vector of the claimed invention. In light of the teachings of the specification such a host cell (and method of modifying the like) is interpreted to read on a host cell *in vivo* (or a method of modifying a host cell *in vivo*) which clearly falls into the realm of gene therapy. However, the skilled artisan would not

be able to rely on the teachings of the specification nor the prior art of record to create a host cell *in vivo* that comprises a heterologous gene under the control of locus control region of the claimed invention for the purpose of providing therapeutic benefit. This is because the art of gene therapy at the time the claimed invention was made was unpredictable and has remained so thereafter. The art of gene therapy is unpredictable with respect to targeting of cells *in vivo*, expression levels of a heterologous nucleotide sequence *in vivo* that correlate with a therapeutic effect, and fate of the expressed heterologous expression product. The specification has provided little guidance or direction to that end. The state of the art of gene therapy is unpredictable with respect to treatment of any disease. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Support for such observations is reflected in two reviews. Verma *et al.* teach that, "there is still no single outcome that we can point to as a success story" (page 239, col. 1). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, col. 3).

Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, col 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (page 30). Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. Furthermore, the specification fails

to teach how to target the appropriate cells for which expression is desired. Targeting of nucleic acid to particular cells was and is a great hurdle in gene therapy. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art, which show promise, but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also

reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Thus in view of the lack of guidance and direction provided by the specification for gene therapy of any disease, it would have required one of skill in the art undue experimentation to make and use the invention as claimed.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28 and 33 are incomplete as written. The preambles of the claims are directed to a process for producing a polypeptide. The steps of the claims do not relate back to the preamble in a positive process to set forth the goal of the claims, which is to produce a polypeptide.

Claim 29 is unclear as written. The claim is directed to a vector for the integration of a heterologous gene into the genome of a mammalian host cell such that the gene may be expressed in the host cell. The claim goes on to require that the vector comprise a transcriptional regulatory sequence, a heterologous gene, and a

locus control region. It would appear from the specification that the heterologous gene should be expressed when the vector is introduced into a host cell. The claim however does not require that the heterologous gene, the transcriptional regulatory sequence (trs) and the locus control region (LCR) be in operable linkage. As such it is unclear how the heterologous gene could be expressed in a host cell if not in operable linkage with the trs and LCR. Claims 30-35 depend from claim 29.

Claim 34 is incomplete as written. The preamble of the claim is directed to a method of modifying mammalian stem cells and progenitor cells. The steps of the claims do not relate back to the preamble in a positive process to set forth the goal of the claims, which is to modify mammalian stem cells and progenitor cells. Claim 35 depends from claim 34.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER